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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/444,281	11/19/1999	JAN BURIAN	660081.411	8461

500 7590 05/14/2004

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EXAMINER	
SCHNIZER, HOLLY G	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 05/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/444,281	BURIAN ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,31,32,35-37,40-42,44,47-51 and 53-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,31,32,35-37,40-42,44,47-51 and 53-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 September 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-8-04 has been entered.

Status of the Claims

The amendment after-final filed December 23, 2003 has been entered. Claims 29, 31-32, 35-37, 40-42, 44, 47-51, and 53-67 are pending.

Rejections Withdrawn

The following rejections given in the previous Office Action mailed October 7, 2003 have been withdrawn.

The rejection of the claims under 35 U.S.C. 112, second paragraph is withdrawn in light of the cancellation and amendment of the claims.

The rejection of the claims under 35 U.S.C. 102(a) as being anticipated by Fraser et al. is withdrawn in light of the cancellation and amendment of the claims.

The rejection of the claims under 35 U.S.C. 102(e) as being anticipated by Krieger et al. is withdrawn in light of the cancellation and amendment of the claims.

Krieger et al. teaches an expression cassette encoding a fusion protein comprising the indolicidin sequence of the present invention (a cationic sequence that has at least 30% tryptophan and has antimicrobial activity) and an anionic sequence wherein the cationic sequence and anionic sequence are separated by a cleavage site. However, Krieger et al. does not specifically state that the structure of the cassette is [(cleavage site)-(cationic peptide)-(cleavage site)-(anionic spacer)].

Rejections

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 29, 32, 40, 45, 47, 48, 49, 50, 51, 53, and 55 are rejected under 35 U.S.C. 102(e) as being anticipated by Selsted et al. (U.S. Patent No. 6,444,645).

Selsted et al. teach an expression cassette that encodes a fusion protein comprising "n" number of repeats of indolicidin analogs (a cationic peptide with at least 30% tryptophan and having antimicrobial activity) separated by methionine (cleavage site) (see Col. 10). Selsted et al. teach that the poly (indolicidin-Met) sequence can be fused to glutathione-S-transferase (GST; an anionic sequence; see Col. 11). Thus, Selsted et al. teach an expression cassette that encodes fusion proteins that have the following structure: (indolicidin)-[(Met)-(Indolicidin)-(Met)-(GST))]. Selsted et al.

indicates that the methionine is a cleavage site cleaved by cyanogens bromide (Col. 11). In addition, GST is an anionic peptide. Since the claims indicate that the encoded fusion protein "comprises" the structure [(cleavage site)-(cationic peptide)-(cleavage site)-(anionic peptide)]n; the structure disclosed in Selsted et al. is encompassed by the claims (wherein n=1). Glutathione-S-transferase is an anionic peptide and therefore would inherently reduce the charge of the cationic peptide. In addition, glutathione-S-transferase is considered a "carrier" peptide. Selsted et al. teaches that the expression cassette can be cloned into an expression vector and expressed in bacterial cells (Col. 7, lines 45-66) and more specifically E. coli (see Col. 16, lines 13-54), to produce the fusion protein (Col. 16, line 13- Col. 17, line 25).

In making the above rejection, the examiner has considered the Declaration under 37 C.F.R. 131 by Daniel Bartfield. The Declaration states that the claimed expression constructs were contemplated before 1998 as evidenced by the pages from a laboratory notebook. However, the claims encompass any construct with the structure (cleavage site)(cationic peptide) (cleavage site) (anionic peptide) whereas the laboratory pages submitted only describe one species of this structure; (cationic peptide)(anionic peptide)(cationic peptide). Moreover, the laboratory pages do not provide any evidence of cleavage sites between the peptides. The laboratory pages only discuss the testing of the specific species disclosed therein and do not suggest that the results from that species can be applied to a more generic form of the expression construct (all cationic peptides and all anionic peptides). Thus, the laboratory pages are considered evidence that the species disclosed therein was contemplated prior to 1998

but not the entire genus claimed. The laboratory pages do not disclose the specific species disclosed in Selsted et al. therefore it appears that there is no evidence that the species disclosed in Selsted et al. was contemplated prior to 1998.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29, 32, 35, 40, 44, 45, 47-51, 53, 55-65, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selsted et al. (U.S. Patent No. 6,444,645) in view of Fraser et al. (U.S. Patent NO. 6, 180,604; Ref. AB of IDS filed 4-23-03).

The applied reference (Fraser et al.) has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it

constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Selsted et al. teach an expression cassette that encodes a fusion protein comprising "n" number of repeats of indolicidin analogs (a cationic peptide with at least 30% tryptophan and having antimicrobial activity) separated by methionine (cleavage site) (see Col. 10). Selsted et al. teach that the poly (indolicidin-Met) sequence can be fused to glutathione-S-transferase (GST; an anionic sequence; see Col. 11). Thus, Selsted et al. teach an expression cassette that encodes fusion proteins that have the following structure: (indolicidin)-[(Met)-(Indolicidin)-(Met)-(GST))]. Selsted et al. indicates that the methionine is a cleavage site cleaved by cyanogens bromide (Col.

11). In addition, GST is an anionic peptide. Since the claims indicate that the encoded fusion protein "comprises" the structure [(cleavage site)-(cationic peptide)-(cleavage site)-(anionic peptide)]n; the structure disclosed in Selsted et al. is encompassed by the claims (wherein n=1). Glutathione-S-transferase is an anionic peptide and therefore would inherently reduce the charge of the cationic peptide. In addition, glutathione-S-transferase is considered a "carrier" peptide. Selsted et al. teaches that the expression cassette can be cloned into an expression vector and expressed in bacterial cells (Col. 7, lines 45-66) and more specifically E. coli (see Col. 16, lines 13-54), to produce the fusion protein (Col. 16, line 13- Col. 17, line 25). Selsted et al. also teaches that the indolicidin analogs can be amidated at the carboxy terminus (Col. 10, line 18).

Selsted et al. does not teach indolicidin analog sequences identical to SEQ ID NOs: 35 or 36 of the present invention. Fraser et al. also does not teach that the encoded protein is expressed in inclusion bodies.

Fraser et al. teaches the expression of indolicidin analogs including indolicidin analogs having sequences identical to SEQ ID NOs: 35 and 36 (see SEQ ID NOs: 30 and 42 of Fraser et al.). Fraser et al. teaches that the analogs are cloned into a vector as a fusion protein with a fusion that is an anionic sequence. The anionic sequence is chosen to protect the bacterial host during expression from the toxic effect of the indolicidin peptide and to transport the fusion peptide to inclusion bodies (Col. 9, lines 17-25). Glutathione-S-transferase (GST) is included as one of the preferred fusion partners (Col. 9, lines 28). Fraser et al. teaches that only the portion of the carrier that is anionic is necessary and not the entire carrier protein (Col. 9, lines 33-35). Fraser et

al. teaches that the promoters used in the expression vector comprising the expression cassette include T7, SP6, tac, and trc (Col. 10, lines 17-20).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use an expression construct for the expression of fusion protein with the structure (cleavage site)-(indolicidin)-(cleavage site)-(GST) as taught in Selsted et al., wherein the expression construct contained the indolicidin sequences taught in Fraser et al. Fraser et al. teaches that the indolicidin sequences taught therein broaden its range and effectiveness (Col. 2, lines 28-33). The selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness (MPEP 2144.07; See also Sinclair & Carroll Co. v. Interchemical Corp. 325 U.S. 327, 65 USPQ 297 (1945)). In the instant case, Fraser et al. provides evidence that a wide variety of indolicidin sequences were known at the time of the invention and could be chosen based on the situation at hand (e.g. the type of organism being treated; see Table 5). For example, the indolicidin sequence identical to SEQ ID NO:35 (SEQ ID NO:30 of Fraser et al.=MBI 11) was more effective in treating A. calcoaceticus than another indolicidin sequence (MBI 10CN; see Table 5, Col. 31, comparing line 34 to line 45). On the other hand, the MBI 10CN sequence was more effective in the inhibition of K. pneumoniae (see Table 5, Col. 31, comparing lines 39 to line 49). In addition, whether or not a protein is expressed in inclusion bodies is an inherent function of the sequence. In the present case, it appears that the indolicidin sequences disclosed in Fraser et al. were inherently expressed in inclusion bodies (see

(Col. 29, Ex. 3, line 60; MBI 11 protein has identical sequence to SEQ ID NO:35 of the present invention).

In making the above rejection, the examiner has considered the Declaration under 37 C.F.R. 131 by Daniel Bartfield. The Declaration states that the claimed expression constructs were contemplated before 1998 as evidenced by the pages from a laboratory notebook. However, the claims encompass any construct with the structure (cleavage site)(cationic peptide) (cleavage site) (anionic peptide) whereas the laboratory pages submitted only describe one species of this structure; (cationic peptide)(anionic peptide)(cationic peptide). Moreover, the laboratory pages do not provide any evidence of cleavage sites between the peptides. The laboratory pages only discuss the testing of the specific species disclosed therein and do not suggest that the results from that species can be applied to a more generic form of the expression construct (all cationic peptides and all anionic peptides). Thus, the laboratory pages are considered evidence that the species disclosed therein was contemplated prior to 1998 but not the entire genus claimed. The laboratory pages do not disclose the specific species disclosed in Selsted et al. therefore it appears that there is no evidence that the species disclosed in Selsted et al. was contemplated prior to 1998.

Claim 66 is rejected under 35 U.S.C. 103(a) as being unpatentable over Selsted et al. and Fraser et al. as applied to claims 29, 32, 35, 40, 44, 45, 47-51, 53, 55-65, and 67 above, and further in view of Rosenburg (Protein Analysis and Purification: Benchtop Techniques, (1996) Birkhauser, pp184-185).

The teachings of Selsted et al. and Fraser et al. have been described above.

Neither Selsted et al. nor Fraser et al. teach cleaving the cationic peptide from the anionic peptide using endoproteinase Lys-C. Selsted et al. discusses placing a methionine between the cationic and anionic carrier sequence for cleavage with cyanogens bromide.

Rosenburg teaches that a wide variety of enzymes were available at the time of the invention for cleaving various specific protein sequences. The selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness (MPEP 2144.07; See also Sinclair & Carroll Co. v. Interchemical Corp. 325 U.S. 327, 65 USPQ 297 (1945)). In the instant case, Rosenburg teaches that there are a variety of enzymes and chemicals that can be used to cleave at specific positions in an amino acid sequence. Endoproteinase lys-C cleaves on the C-terminal side of lysines (see Table 8.1). As evidenced by Rosenburg, endoproteinase lys-C was well known in the art and readily available at the time of the invention. It would have been obvious to one of ordinary skill in the art at the time of the invention to choose endoproteinase lys-C when the cationic peptide used was SEQ ID NOs: 30 or 42 of Fraser et al. since the C-terminal amino acid of these sequences is lysine.

Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Selsted et al. (U.S. Patent No. 6,444,645) and Fraser et al. as applied to claims 29, 32, 35, 40, 44, 45, 47-51, 53, 55-65, and 67 above, and further in view of Shen (Proc. Natl. Acad. Sci (1984) 81: 4627-4631; ref. BH of IDS of Paper No. 9), Stratagene Catalog (1993),

pp. 38, 44, and 48; cited in Notice of References cited of 1-23-03), the Pharmacia Product Catalog (1996; pp. 110 and 121-123; cited in Notice of References cited 1-23-03), and Sambrook et al. (Molecular Cloning: A laboratory Manual, 1989, Cold Spring Harbor Laboratory Press, p. 1.14-1.15; cited in Notice of References cited of 1-23-03).

Selsted et al. teach an expression cassette that encodes a fusion protein comprising "n" number of repeats of indolicidin analogs (a cationic peptide with at least 30% tryptophan and having antimicrobial activity) separated by methionine (cleavage site) (see Col. 10). Selsted et al. teach that the poly (indolicidin-Met) sequence can be fused to glutathione-S-transferase (GST; an anionic sequence; see Col. 11). Thus, Selsted et al. teach an expression cassette that encodes fusion proteins that have the following structure: (indolicidin)-[(Met)-(Indolicidin)-(Met)-(GST))]. Selsted et al. indicates that the methionine is a cleavage site cleaved by cyanogens bromide (Col. 11). In addition, GST is an anionic peptide. Since the claims indicate that the encoded fusion protein "comprises" the structure [(cleavage site)-(cationic peptide)-(cleavage site)-(anionic peptide)]n; the structure disclosed in Selsted et al. is encompassed by the claims (wherein n=1). Glutathione-S-transferase is an anionic peptide and therefore would inherently reduce the charge of the cationic peptide. Selsted et al. teaches that the expression cassette can be cloned into an expression vector and expressed in bacterial cells (Col. 7, lines 45-66) and more specifically E. coli (see Col. 16, lines 13-54), to produce the fusion protein (Col. 16, line 13- Col. 17, line 25).

Selsted et al. describes recombinant expression of the expression construct but does not specifically provide the promoters used in that expression.

Shen et al. teach that lac and tac promoters can be used successfully in the high level expression of proteins from cassettes containing multiple copies of coding sequences.

The Stratagene Catalog, Pharmacia Catalog, and Sambrook et al. provide evidence that the promoters listed I claim 31 were well known in the art and readily available at the time of the invention.

MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp. 325 U.S. 327, 65 USPQ 297 (1945). In the instant case, Shen et al., Sambrook et al., and the Pharmacia and Stratagene Catalogs teach that there are a variety of promoters that can be used in the recombinant expression of proteins. As evidenced by Shen et al. Sambrook et al., and the Pharmacia and Stratagene catalogs, the promoters of Claim 31 were well known in the art and readily available at the time of the invention. It would have been obvious to one of ordinary skill in the art at the time of the invention that any one of these promoters could be used in the vectors disclosed in Selsted et al. One would have selected the promoter depending on the materials (host cells, vectors, induction materials such as IPTG) available in the laboratory. Thus, Claim 31 is unpatentable over the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Tuesday, Thursday, and Friday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
May 13, 2004

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